

Maternal and Fetal Immune Responses to In Utero Hematopoietic Stem Cell Transplantation

Grant Award Details

Maternal and Fetal Immune Responses to In Utero Hematopoietic Stem Cell Transplantation

Grant Type: Transplantation Immunology

Grant Number: RM1-01718

Project Objective: Objective is to study the maternal and fetal immune responses to in utero hematopoietic stem cell transplantation in mouse models and human patients.

Investigator:

Name:	Tippi MacKenzie
Institution:	University of California, San Francisco
Type:	PI

Disease Focus: Pediatrics, Immune Disease, Blood Disorders

Human Stem Cell Use: Other

Award Value: \$1,230,869

Status: Closed

Progress Reports

Reporting Period: Year 1

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Reporting Period: Year 3

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Reporting Period: NCE

Grant Application Details

Application Title:	Maternal and Fetal Immune Responses to In Utero Hematopoietic Stem Cell Transplantation
Public Abstract:	<p>The immune system is the body's defense system against disease and can recognize foreign cells. Because of this, stem cells and organs that are transplanted from one person to another are usually "rejected" by the immune system, forcing doctors to use powerful immune suppressive drugs with severe side effects. This natural defense system will therefore limit our ability to use stem cell therapies until we develop better solutions to prevent rejection ("induce tolerance").</p> <p>We are developing a unique solution to this problem: if we transplant cells in utero, before the immune system is fully developed, we can educate the fetus to tolerate the foreign cells and avoid rejection without using any drugs. This strategy could be useful for many inherited stem cell disorders such as sickle cell disease, thalassemias, and muscular dystrophy. In addition, if tolerance to a particular donor is established, it may be used to transplant an organ (eg. kidney) from the same donor for other congenital anomalies. Many of these diseases can be diagnosed early in pregnancy and the surgical expertise for performing the transplants safely already exists.</p> <p>Although this strategy has been successful in animal models, cells transplanted in utero have mostly been rejected and we have been doing research to improve these results. Our lab has recently made the important discovery that the mother's immune system is also responsible for rejection: we believe that cells from the mother help the immature fetal immune system develop faster and facilitate rejection of the transplanted cells. In this proposal, we will study this idea in both an animal model and in patients who have fetal surgery for other diseases. We will examine whether surgery leads to changes in the mother and fetus which prompt rejection of the transplanted cells.</p> <p>The strategy of treating stem cell disorders in utero to avoid rejection has a high likelihood of success and our team is uniquely qualified to perform a clinical trial of in utero stem cell transplantation once we have evidence of safety and efficacy in animal models. The experiments in this proposal will give us important information to design innovative treatments for common, currently incurable stem cell disorders.</p>

Statement of Benefit to California:

The long term goal of our team is to develop strategies for safe and effective stem cell transplants to cure fetuses with congenital stem cell disorders. Many common diseases can be diagnosed early in pregnancy and may potentially be treated with in utero stem cell transplantation. For example, blood stem cells may be used to treat sickle cell disease and thalassemias. Muscle stem cells may be used to treat muscular dystrophies and liver stem cells may be used to treat metabolic disorders. Furthermore, transplantation of blood stem cells may be used to develop tolerance to a particular donor so that organs can be transplanted without immunosuppression. Recent progress in our understanding of immune interactions between the mother and fetus has brought us closer to realizing this goal.

Congenital stem cell disorders are common and affect many patients in California. For example, hemoglobin disorders are so common that they are routinely screened in all babies (and prenatal diagnosis can be done if there is a family history): each year, 2000 children are born with sickle cell disease in the United States, 150 children in California alone (www.scdcf.org). Thalassemias are found more commonly in persons of Mediterranean or Asian descent and are therefore prevalent in our state's population. Muscular dystrophy affects 1/3500 births and currently has no cure while inborn errors of metabolism affect 1/4000. Given that more than 500,000 children are born each year in California, the potential to make a difference is enormous. Furthermore, our studies will improve our knowledge about the uniquely tolerant state of the fetus and may allow us to then design treatments to improve tolerance in adult patients.

in utero surgery was born in California and is performed in only select centers in the country. Therefore, once we have developed safe and effective therapies for stem cell disorders, we also expect increased referrals of such patients to California. The convergence of our expertise in fetal therapies with those in stem cell biology carries great promise for finally realizing the promise of in utero stem cell transplantation.

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